Anti-Allergens Oral
Therapeutic Class Review (TCR)

June 15, 2015

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

FDA-APPROVED INDICATIONS

Drug Name	Manufacturer	Indication(s)
Short ragweed (*Ambrosia artemisiifolia)* pollen allergen extract (Ragwitek™)[1]	Merck Sharp & Dohme	Immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for short ragweed pollen in adults 18 years through 65 years of age.
Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass mixed pollens allergen extract (Oralair®)[2]	Greer	Immunotherapy for the treatment of grass pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the five grass species contained in this product in persons 10 years through 65 years of age.
Timothy grass (*Phleum pratense*) pollen allergen extract (Grastek®)[3]	Merck Sharp & Dohme	Immunotherapy for the treatment of grass pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens in persons 5 years through 65 years of age.

OVERVIEW

Allergic rhinitis (hay fever), with or without allergic conjunctivitis, affects approximately 30 million people in the United States (U.S.). Allergen avoidance and medication therapy can provide significant symptom relief, but for many, symptoms still remain.[4] For some of these patients, allergen immunotherapy is a reasonable alternative. Subcutaneous immunotherapy (SCIT) has proven to be effective in the management of allergic rhinitis and asthma since the early 20th century; however, it requires regular injections, typically over a period of three to five years, and carries the potential of serious systemic allergic reactions in response to the treatment itself. Until 1991, patient-specific allergen vaccines were used.[5] In 1998, the World Allergy Organization (WAO) stated that the cumulative evidence showed sublingual allergen immunotherapy (SLIT) to be an appropriate alternative to SCIT.[6] SLIT use has been widely accepted in Europe, South America, Asia, and Australia. In 2014, it gained Food and Drug Administration (FDA) approval for use in the U.S.[7]

The 2011 American Academy of Allergy, Asthma, and Immunology (AAAAI) practice parameters on allergen immunotherapy stress the importance of appropriate indications, the absence of significant comorbid conditions, and the patient's ability to comply with allergen immunotherapy.[8] SLIT was still considered investigational in the U.S. at the time of this publication. AAAAI states that, in general, most studies demonstrated that SLIT is safe and effective; however, variations in effectiveness have been attributed to the differences in the dose of allergen used. In general, the higher doses of allergen appeared to have a greater impact on symptom improvement.[9] In addition, for the sublingual route, much higher doses are required, compared to the subcutaneous route.[10]

The 2015 American Academy of Otolaryngology – Head and Neck Surgery practice guidelines for allergic rhinitis state that clinicians should offer immunotherapy (SLIT or SCIT) for patients who have an inadequate response to pharmacologic therapy, with or without environmental controls, and that both forms of immunotherapy have been proven effective in reducing symptoms.[11] The guidelines add that potential indications for considering immunotherapy include patient preference, adherence, adverse effects of other medications, coexisting allergic asthma, and possible prevention of asthma. The guidelines also mention that there may be long-term cost savings with immunotherapy, and that there is ongoing debate as to which form of immunotherapy is superior.

Allergen-specific immunotherapy, including SLIT, may reduce the onset of new sensitizations, and reduce the onset of asthma, although SLIT is not appropriate as monotherapy for the treatment of asthma.[12] According to the World Allergy Organization (WAO) 2013 update of their Sublingual Allergen position paper, improvement in allergic rhinitis persists for one to two years after discontinuation of three years of SLIT with grass pollen extract. A small double-blind, double-dummy study in grass pollen allergic patients showed that the clinical efficacy of SLIT was equivalent to that of SCIT as measured by symptoms and medication use ($p<0.01$). The current challenge is to identify those patients who are most likely to benefit from the administration of SLIT. Patients should have a history of symptoms related to allergen exposure and have a documented positive allergen-specific IgE test. Mono- and polysensitized patients benefit equally well from allergy immunotherapy. WAO suggests that patients in whom pharmacotherapy does not control allergy symptoms or induces undesirable side effects or patients who refuse injections or long-term pharmacotherapy may benefit most from SLIT. WAO advises that SLIT should only be prescribed by physicians with appropriate allergy training and expertise. In general, SLIT appears to be associated with fewer and less severe adverse effects as compared to SCIT.

PHARMACOLOGY

SCIT suppresses allergic Th2-mediated inflammation and increases antigen-specific IgG, probably by induction of regulatory T cells (Tregs), immune deviation (Th2 to Th1), and/or apoptosis of effector memory Th2 cells.[13] SLIT induces modest systemic changes consistent with SCIT, but additional local mechanisms in the oral mucosa and/or regional lymph nodes are likely important.

The oral mucosa is a natural site of immune tolerance. Once the allergen is absorbed, the systemic mechanism(s) of SLIT is thought to be similar to SCIT; however, prior to sublingual absorption, the mechanism differs.[14,15,16] Allergen extracts cross the sublingual mucosa, where the allergen molecules are captured by dendritic cells. Within 24 to 48 hours, the dendritic cells migrate to draining cervical lymph nodes and tonsils where they present allergen-derived peptides to native T cells. Within a few days, Treg cells differentiate from naive T cells and exert a suppressive effect on both Th1 and Th2 responses. A production of IL-10 with resulting down-modulation of the immune response has also been reported. In the sublingual mucosa, mast cells, basophils, and eosinophils are less numerous. This characteristic of the oral mucosa is believed to contribute to the lower rates of adverse systemic allergic reactions seen with SLIT.

Subcutaneous and sublingual immunotherapy cause early increases in allergen-specific IgE and blunting of seasonal allergen-specific IgE.[17] In addition, they lead to persistent increases in antigen-specific immunoglobulin G4 (IgG4).

CONTRAINDICATIONS/WARNINGS[18,19,20]

The agents in this review are contraindicated in patients with severe, unstable, or uncontrolled asthma, a history of any of the following: severe systemic allergic reaction, severe local reaction after taking any sublingual allergen immunotherapy, or hypersensitivity to any inactive ingredient in the product.

Eosinophilic esophagitis has been reported in association with SLIT. If severe or persistent gastro-esophageal symptoms, such as dysphagia or chest pain, occur, discontinue SLIT and evaluate for eosinophilic esophagitis. Interrupt SLIT in patients with oral inflammation or oral wounds. Allow for complete healing before restarting therapy. All three agents are contraindicated in patients with a history of eosinophilic esophagitis.

Boxed warnings include life-threatening systemic and local allergic reactions, including anaphylaxis and laryngopharyngeal edema, and may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. These conditions include markedly compromised lung function, unstable angina, recent myocardial infarction, arrhythmia, and uncontrolled hypertension.

Patients should be observed in a healthcare setting for at least 30 minutes following the initial dose. Auto-injectable epinephrine should be prescribed and the patient should be trained on its appropriate use. SLIT therapy may not be suitable for patients who may be unresponsive to inhaled bronchodilators or epinephrine, such as those receiving beta-blocker, alpha-adrenergic blockers, or ergot alkaloids. In addition, the adverse effects of epinephrine may be potentiated by tricyclic antidepressants, levothyroxine, monoamine oxidase inhibitors (MAOIs), cardiac glycosides, and certain antihistamines.

SLIT has not been studied in people with moderate to severe asthma or those requiring daily medication to treat asthma. In addition, SLIT should be withheld in patients with an acute asthma exacerbation. SLIT has not been studied with concomitant allergen immunotherapy which may increase the risk of local or systemic side effects.

The manufacturers of Oralair advise that the risks of adverse effects may be increased when treatment is initiated during the grass pollen season.

The agents in this review are not indicated for the immediate relief of allergy symptoms.

DRUG INTERACTIONS[21,22,23]

No clinically relevant drug-drug interactions have been reported.

ADVERSE EFFECTS

Local reactions, primarily oral-mucosal in nature, are common with SLIT, most of which are reported to be mild to moderate in severity and subside with continued treatment.[24] No clear risk factors for adverse effects of SLIT have been identified. Tolerability may vary with the type of extract and formulation. SLIT dose has not clearly been correlated to rate or severity of adverse effects. An accelerated induction schedule has not shown to be associated with a greater risk of systemic adverse reactions with SLIT, as with SCIT; however, most adverse effects reported occurred during the induction phase. In clinical studies, most patients with SLIT-related serious adverse reactions had asthma; symptomatic asthma has been identified as a risk factor for SCIT adverse effects. Case reports

have suggested that SLIT carries the same risk factors as SCIT, including height of season and history of previous systemic reaction.

Adverse reactions reported in at least 5% of patients in clinical studies with the agents in this review include oral pruritus, throat irritation, ear pruritus, mouth edema, and tongue pruritus.[25,26,27]

SPECIAL POPULATIONS[28,29,30]

Pediatrics

Safety and efficacy have been established in patients at least five years of age for Grastek and at least ten years of age for Oralair. Safety and efficacy of Ragwitek have not been established in pediatric patients.

Safety studies in young children reported that most adverse reactions were mild or moderate and resolved without treatment.[31]

Pregnancy

Oralair and Grastek are Pregnancy Category B agents; Ragwitek is Category C.

AAAAI and WAO advise that allergen immunotherapy can be continued, but usually is not initiated in the pregnant patient. [32,33]

Geriatric

Safety and efficacy of Grastek, Oralair, and Ragwitek have not been established in patients over 65 years of age.

Ragwitek was not studied for efficacy in subjects 51 years of age and older. However, the Allergenic Products Advisory Committee (APAC) stated that there is no reason why subjects more than 50 years of age would respond differently to Ragwitek than other adult subjects less than 50 years of age and the FDA considers the existing efficacy data adequate to support use of Ragwitek in adults 51 through 65 years of age.[34]

DOSAGE AND ADMINISTRATION

Drug	Indication/Dosages	Package size
Short ragweed pollen allergen extract (Ragwitek)[35]	1 tablet administered sublingually once daily	Sublingual tablet: Amb a 1-Unit 30 and 90 tablet packages
Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract (Oralair)[36]	**Adults:** 300 index of reactivity (IR) administered sublingually once daily **Pediatrics:** 100 IR once daily on Day 1; 2 x 100 IR once daily on Day 2; then 300 IR once daily thereafter.	Sublingual tablets: 100 IR and 300 IR Adult starter pack: three 300 IR tablets Pediatric starter pack: three 100 IR tablets Commercial pack: thirty 300 IR tablets
Timothy grass pollen allergen extract (Grastek)[37]	1 tablet administered sublingually once daily	Sublingual tablet: 2800 bioequivalent allergy unit (BAU) 30 tablet package

The first dose of SLIT should be administered in a healthcare setting to observe for acute allergic reactions and treated if they occur. Observe patients for at least 30 minutes after administration. SLIT should be administered to children under adult supervision.

The sublingual tablets should be removed from the blister with clean dry hands just prior to dosing and placed immediately under the tongue until complete dissolution for at least one minute before swallowing. To avoid swallowing, food or beverage should not be taken for five minutes following dissolution of the tablet. Wash hands after handling the sublingual tablet.

Initiate Oralair treatment at least 16 weeks before, and Grastek and Ragwitek treatment at least 12 weeks before the expected onset of the corresponding allergen season. SLIT should be continued throughout the allergen season. For sustained effectiveness for one grass pollen season after cessation of treatment, Grastek may be taken daily for three consecutive years, including the intervals between the grass pollen seasons. Studies have demonstrated that, during the first two years of co-seasonal or continuous dosing, SLIT with grass pollen extract efficacy was more pronounced with the continuous use; however, after three years of therapy, both treatment regimens were equally effective in reducing allergy symptoms.[38]

Data regarding the safety of starting treatment during the pollen season or restarting treatment after missing a dose of Oralair, Grastek, and Ragwitek are lacking. However, in the clinical trials for Grastek and Ragwitek, treatment interruptions for up to seven days were allowed.

Patients receiving SLIT should be prescribed and properly trained on auto-injectable epinephrine for emergency use.

CLINICAL TRIALS

Search Strategy

Search strategy included the use of all drugs in this class and the FDA-approved indications. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance. Limited comparative clinical trials were found.

Rhinoconjunctivitis Total Symptom Score (RTSS) or Rhinoconjunctivitis daily symptom scores (DSS): the total of six symptom scores (e.g., sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes). Each score ranges from 0 to 3 (absent, mild, moderate, severe); the maximum RTSS is 18.[39,40,41]

Daily Medication Score (DMS) or Daily Rescue Medication Score (RMS): accounts for the use of allowed rescue medication by subjects based on the following scale that assumes increasing effectiveness among medication types: 0=absent, 1=antihistamine, 2=nasal corticosteroid, 3=oral corticosteroid.

Total Combined Score (TCS): the sum of each daily symptom score (DSS) and daily medication score (DMS) divided by total number of days of the grass pollen season (GPS). The maximum TCS is 54.

Daily Combined Score (CS): the mean of the RTSS and RMS giving equal weight to symptoms and medication use. The CS ranges from 0 to 3.

The FDA considers the point estimate of the improvement of 15% over placebo and an upper limit of the 95% CI of < -10% as clinically significant.

Short Ragweed Pollen Allergen Extract (Ragwitek)[42,43]

Two double-blind, placebo-controlled clinical trials in adults ages 18 through 50 years evaluated the efficacy of Ragwitek in the treatment of ragweed pollen-induced allergic rhinitis, with or without conjunctivitis. Approximately 16% of subjects had mild asthma and about 81% were sensitized to other allergens in addition to ragweed at baseline. Patients (n=767) received Ragwitek or placebo for approximately 12 weeks prior to the start of the ragweed pollen season and throughout the ragweed pollen season. Patients were allowed to take medications, including systemic and topical antihistamines and topical and oral corticosteroids, as needed for symptom relief. Patients self-reported DSS and DMS. The primary endpoint, TCS, was averaged over the peak ragweed pollen season and also averaged over the entire ragweed season. In both studies, relative to placebo, subjects in the Ragwitek group experienced a decrease in TCS during the peak ragweed season (Trial 1: -26%, 95% CI -38.7, -14.6; Trial 2: -24%, 95% CI -36.5, -11.3) and a decrease in the average TCS from the start of and

throughout the entire ragweed pollen season (Trial 1: -26%, 95% CI -37.6, -13.5; Trial 2: -27%, 95% CI -38.8, -14.1). Decreases relative to placebo were also seen in DSS and DMS in the Ragwitek group.

Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract (Oralair)[44,45]

In a study conducted in U.S., 473 adults aged 18 through 65 years with a positive skin prick test to Timothy grass pollen extract received Oralair or placebo, starting approximately four months prior to the expected onset of the grass-pollen season and continuing for the duration of one pollen season. The primary objective was to assess the safety and efficacy of Oralair 300 IR during the grass pollen season. The primary efficacy endpoint parameter was the CS. The Relative Difference, as calculated as the LS mean difference between Oralair and placebo divided by the LS mean of placebo, expressed as a percentage, between Oralair and placebo of the daily CS was -28.2% (95% CI -43.4%;-13%), daily RTSS was -22.9% (95% CI -38.2%;-7.5%), and daily RMS was -46.5% (95% CI -73.9%;-19.2%).

In a similar European study, 311 adults aged 18 to 45 years with a positive skin prick test to 5-grass pollen extract and positive *in vitro* testing for timothy grass-specific serum IgE received one of three different doses of Oralair or placebo starting approximately four months prior to the expected onset of the grass pollen season and continuing for the duration of one grass pollen season. The Oralair group was dosed 100 IR on Day 1, 200 IR on Day 2, and 300 IR on each day thereafter. The relative difference between Oralair and placebo of the daily CS was -29.6% (95% CI -43.1%;-16.1%), daily RTSS was -29.2% (95% CI -43.4%;-15.1%), and daily RMS was -30.1% (95% CI -49.5%;-10.6%).

In a long-term study, a total of 426 adults received Oralair or placebo starting approximately four months prior to the grass pollen season and continuing for the entire season. Subjects were treated for three consecutive grass pollen seasons (Year 1 to Year 3). The primary evaluation was the Year 3 pollen period. Participants then entered two years of immunotherapy-free follow-up (Year 4 and Year 5). The results of the analysis of the daily Combined Score for Oralair for treatment Years 1 through 3 were -16.4% (95% CI -27%; -5.8%), -38% (95% CI -53.4%; -22.6%), and -38.3% (95% CI -54.7%; -22.0%), respectively. Data were insufficient to demonstrate efficacy for one or two years after discontinuation of immunotherapy.

In a pediatric study, 278 children and adolescents were randomized to receive either placebo or Oralair for four months prior to the onset of, and throughout one grass pollen season. The Oralair group was dosed 100 IR on Day 1, 200 IR on Day 2, and 300 IR on each day thereafter. The results of the daily CS, daily RTSS and daily RMS were -30.1% (95% CI 46.9%;-13.2%), -30.6% (95% CI -47%; -14.1%), -29.5% (95% CI -50.9%; -8%), respectively.

Timothy Grass Pollen Allergen Extract (Grastek)[46,47]

Two 24-week randomized, double-blind, parallel group, clinical trials evaluated the efficacy of Grastek during the first grass pollen season. Subjects, five years of age and older, had a history of grass pollen-induced rhinitis, with or without conjunctivitis, and sensitivity to Timothy grass pollen as determined by specific testing (IgE). Twenty-five percent of subjects had mild, intermittent asthma and 85% were sensitized to other allergens in addition to grass pollen. Subjects initiated Grastek (n=752) or placebo (n=749) approximately 12 weeks prior to the pollen season. Symptom-relieving medications were allowed, as needed. Subject self-reported rhinoconjunctivitis daily symptom scores (DSS), measured on a scale of 0 (none) to 3 (severe), and daily medication scores (DMS). The sums of DSS and DMS were

combined into the Total Combined Score (TCS) and averaged over the entire grass pollen season. The percent change in TCS during the entire grass pollen season in the Grastek group relative to the placebo group was -23.2% (95%CI -36.0;-13.0). Similarly, the DSS and DMS were decreased in those treated with Grastek compared to placebo throughout the grass pollen season (DSS -20%, 95%CI -32;-10; DMS -35%, 95% CI -49.3;-20.8), and the TCS was decreased compared to placebo during the peak grass pollen season (-29%, 95% CI -39.0;-15).

The sustained effect of Grastek was evaluated in one five-year, double-blind study. The study design was similar to that of the 24-week studies. Subjects (n=634) received Grastek or placebo daily for three consecutive years and were followed for two years without treatment. Subjects treated with Grastek had a decrease in TCS throughout the grass pollen season during the three years of active treatment (difference relative to placebo: -34.2 and -40.9% in treatment years one and two, respectively). This effect was sustained during the grass pollen season in the first year after discontinuation of Grastek (difference relative to placebo: -34%), but not in the second year (difference relative to placebo: -27.2%).

SUMMARY

Subcutaneous immunotherapy (SCIT) has proven to be effective in the management of allergic rhinitis and asthma; however, it requires regular injection and is associated with the risk of serious systemic allergic reactions in response to the treatment itself. Sublingual immunotherapy (SLIT) offers several specific advantages over injection immunotherapy in that it can be self-administered by patients or caregivers, does not require injections, and carries a much lower risk of anaphylaxis compared with SCIT.

The clinical efficacy of SLIT has been shown to be equivalent to that of SCIT as measured by symptoms and medication use. Improvement in allergic rhinitis has been reported to persist for one to two years after discontinuation of three years of treatment with SLIT with grass pollen extract. Common adverse effects reported are primarily oral-mucosal in nature, most of which are mild to moderate in severity and subside with continued treatment.

The first products for SLIT have recently been approved in the U.S. for the management of grass/ragweed pollen allergies. These include Ragwitek (Short Ragweed Pollen Allergen Extract) for use in adults, Grastek (Timothy Grass Pollen Allergen Extract), and Oralair (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract) approved for use in adults and pediatrics. These agents are dosed sublingually once daily and continuing throughout the allergen season, Oralair beginning 16 weeks and Grastek and Ragwitek 12 weeks before the corresponding anticipated allergen season. The first dose of SLIT should be given in a healthcare setting; subsequent doses may be self-administered by the patient or caregiver.

REFERENCES

1 Ragwitek [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; June 2014.
2 Oralair [package insert]. Lenoir, NC; Greer Laboratories; October 2014. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenics/UCM391580.pdf. Accessed June 16, 2015.
3 Grastek [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; April 2014.
4 Summary Basis for Regulatory Action: Grastek. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenics/UCM394272.pdf. Accessed June 16, 2015.
5 Bousquet J, Casale T, Lockey RF, et al. Sub-lingual immunotherapy: World Allergy Organization position paper 2009. Available at: http://www.waojournal.org/content/pdf/1939-4551-2-11-233.pdf. Accessed June 16, 2015.
6 Canonica W, Bousquet J, Casale T, et al. Sub-lingual immunotherapy: World Allergy Organization position paper 2009. World Allergy Organization Journal. 2009;2(11):223-281. Available at: http://www.waojournal.org/content/pdf/1939-4551-2-11-233.pdf. Accessed June 16, 2015.
7 Summary Basis for Regulatory Action: Grastek. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenics/UCM394272.pdf. Accessed: June 16, 2015.
8 Cox L, Nelson H, Lockey R. et al. Allergen immunotherapy: A practice parameter third update. Available at: http://www.aaaai.org/practice-resources/Statements-and-Practice-Parameters/Practice-parameters-and-other-guidelines-page.aspx. Accessed June 16, 2015.
9 Available at: http://www.aaaai.org/conditions-and-treatments/library/allergy-library/sublingual-immunotherapy-for-allergic-rhinitis.aspx. Accessed June 16, 2015.
10 Cox L, Nelson H, Lockey R. et al. Allergen immunotherapy: A practice parameter third update. Available at: http://www.aaaai.org/practice-resources/Statements-and-Practice-Parameters/Practice-parameters-and-other-guidelines-page.aspx. Accessed June 16, 2015.
11 Seidmna, M, Gurgel, R, Lin, S, et al. Clinical Practice Guideline: Allergic Rhinits. Available at: http://www.entnet.org/content/aao-hnsf-clinical-practice-guideline-allergic-rhinitis. Accessed July 6, 2015.
12 Canonica GW, Cox W, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organization Journal 2014, 7:6. Available at: http://www.waojournal.org/content/7/1/6. Accessed June 16, 2015.
13 Canonica GW, Cox W, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organization Journal 2014, 7:6. Available at: http://www.waojournal.org/content/7/1/6. Accessed June 16, 2015.
14 Cox L. Sublingual immunotherapy for aeroallergens: Status in the United States. Allergy Asthma Proc 35:34 –42, 2014; doi: 10.2500/aap.2014.35.3708.
15 Hovav AH. Dendritic cells of the oral mucosa. Mucosal Immunology (2014) 7, 27–37; doi:10.1038/mi.2013.42. Available at: http://www.nature.com/mi/journal/v7/n1/full/mi201342a.html. Accessed June 16, 2015.
16 Frati F, Moingeon P, Marcucci F. Mucosal immunization application to allergic disease: Sublingual immunotherapy. Allergy and Asthma Proceedings. 2007:28(1);35-39.
17 Canonica GW, Cox W, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organization Journal 2014, 7:6. Available at: http://www.waojournal.org/content/7/1/6. Accessed June 16, 2015.
18 Ragwitek [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; June 2014.
19 Oralair [package insert]. Lenoir, NC; Greer Laboratories; October 2014.
20 Grastek [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; April 2014.
21 Ragwitek [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; June 2014.
22 Oralair [package insert]. Lenoir, NC; Greer Laboratories; October 2014.
23 Grastek [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; April 2014.
24 Canonica GW, Cox W, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organization Journal 2014, 7:6. Available at: http://www.waojournal.org/content/7/1/6. Accessed June 16, 2015.
25 Ragwitek [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; June 2014.
26 Oralair [package insert]. Lenoir, NC; Greer Laboratories; October 2014.
27 Grastek [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; April 2014.
28 Ragwitek [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; June 2014.
29 Oralair [package insert]. Lenoir, NC; Greer Laboratories; October 2014.
30 Grastek [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; April 2014.
31 Canonica GW, Cox W, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organization Journal 2014, 7:6. Available at: http://www.waojournal.org/content/7/1/6. Accessed June 16, 2015.
32 Cox L, Nelson H, Lockey R. et al. Allergen immunotherapy: A practice parameter third update. Available at: http://www.aaaai.org/practice-resources/Statements-and-Practice-Parameters/Practice-parameters-and-other-guidelines-page.aspx. Accessed June 16, 2015.
33 Canonica GW, Cox W, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organization Journal 2014, 7:6. Available at: http://www.waojournal.org/content/7/1/6. Accessed June 16, 2015.
34 Summary Basis for Regulatory Action: Ragwitek. Available at: http://www.fda.gov/BiologicsBloodVaccines/Allergenics/ucm397087.htm. Accessed June 16, 2015.
35 Ragwitek [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; June 2014.
36 Oralair [package insert]. Lenoir, NC; Greer Laboratories; October 2014. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenics/UCM391580.pdf. Accessed June 16, 2015.
37 Grastek [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; April 2014.
38 Canonica GW, Cox W, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organization Journal 2014, 7:6. Available at: http://www.waojournal.org/content/7/1/6. Accessed June 16, 2015.
39 Summary Basis for Regulatory Action: Ragwitek. Available at: http://www.fda.gov/BiologicsBloodVaccines/Allergenics/ucm397087.htm. Accessed June 16, 2015.
40 Summary Basis for Regulatory Action: Oralair. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenics/UCM393021.pdf. Accessed June 16, 2015.

41 Summary Basis for Regulatory Action: Grastek. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenics/UCM394272.pdf . Accessed June 16, 2015.
42 Ragwitek [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; June 2014.
43 Summary Basis for Regulatory Action: Ragwitek. Available at: http://www.fda.gov/BiologicsBloodVaccines/Allergenics/ucm397087.htm. Accessed June 6, 2015.
44 Oralair [package insert]. Lenoir, NC; Greer Laboratories; October 2014. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenics/UCM391580.pdf. Accessed June 6, 2015.
45 Summary Basis for Regulatory Action: Oralair. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenics/UCM393021.pdf. Accessed June 6, 2015.
46 Grastek [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme; April 2014.
47 Summary Basis for Regulatory Action: Grastek. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenics/UCM394272.pdf. Accessed June 6, 2015.